Supervoltage Radiation Therapy

Use of the Linear Accelerator for Treating Ovarian Adenocarcinoma

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■ *In a study of patients treated thus far by supervoltage radiation from the Stanford linear accelerator, the following conclusions were reached:*

Homogenous radiation in doses of 4,000 rads may be delivered to the upper abdomen and 5,500 rads to the lower abdomen and pelvis for the treatment of ovarian cancer by the proper utilization of modern supervoltage radiation sources.

Patients with Stage 2 and Stage 3 lesions are best treated by total hysterectomy and bilateral salpingo-oophorectomy followed by total pelvic irradiation.

Stage 4 disease was seldom controlled by high dose radiation therapy to the entire peritoneal cavity.

An unusual histologic pattern has been found in the liver of three patients who died three to nine months after 4,000 to 5,000 rads had been given in a period of five or six weeks.

THE NATURAL HISTORY of carcinoma of the ovary is sufficiently variable to make evaluation of treatment difficult. Many methods of treatment have been advocated but no prospective controlled study evaluating these proposals has been reported; the results presented to date are not so different as to allow an obvious choice of a preferred method of treatment. The present report is of results of treating a group of patients with this disease in a uniform manner with supervoltage radiotherapy.

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In order to be able to compare our data with the most recent and exhaustive reports, we have adopted the staging classification proposed by Rubin (Table 1).[10]

Present Series

The present series consists of 63 patients (Chart 1) seen in the Division of Radiotherapy at the Stanford Medical Center between the institution of treatment with the Stanford medical linear accelerator in January, 1956, through June, 1962. Referrals from private gynecologists and from the Stanford University Gynecological Service have

been considered, but there has been no established referral policy and these cases do not represent all of the cases seen at the Stanford Medical Center. No Stage I cases have been referred. An occasional patient with an advanced lesion has not been referred because of the philosophy of the attending physician. In all cases the lesions were proven histologically and no patient has been lost to follow-up. The age distribution is shown in Chart 2, the peak incidence occurring at age 51-55.

Treatment Program

The treatment program is as follows:

Surgical. Total abdominal hysterectomy with bilateral salpingo-oophorectomy is the primary treatment. Should widespread disease be discovered at the time of laparotomy, as much as possible of the primary and metastatic tumor is removed. We do not subscribe to the policy of leaving the uterus in place as a radium carrier.[2,8]

Radiotherapy. The 4.8 million electron volt (MEV) Stanford medical linear accelerator* was installed in 1955, and treatment with it was begun in January 1956. Details of its operation have been reported.[5,6,12,13] The decrease in skin reaction, bone absorption and integral dose induced us to attempt delivery of a homogenous dose of radiation throughout the entire volume of involvement. Sharp beam definition and accurate shielding enabled us to accomplish this while sparing vital organs such as the kidney. As there is no clinical or radiobiological data to indicate that cure of ovarian adenocarcinoma is possible with low doses of irradiation, the program has been to deliver as large a tumor dose as was considered feasible without undue risk of damage to vital organs.

*The usual operating energy has been 4.8 million electron volts (MEV).

Stage	Histologic Classification A	B	C	D	E	Total
I						0
II	●●●	●●●	●●			8
III	●●●● ●●●	●●●●	●●●●		●●●	18
IV	●●●● ●●●● ●●●● ●	●●●● ●●●● ●●●● ●●●● ●	●●		●●	34
Total	23	24	8	0	5	60

Chart 1.—Distribution of patients with carcinoma of the ovary, by stage and histologic classification.

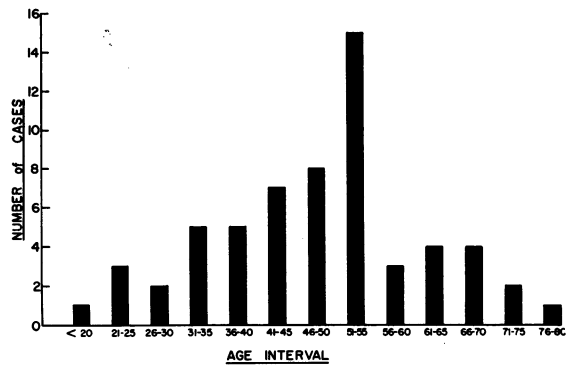


Chart 2.—Age distribution (in years) of patients treated for carcinoma of the ovary with supervoltage x-radiation.

Data on the treatment of various stages of disease follow:

Stage 1. No Stage 1 cases were referred. It does not seem logical to add the risks of radiation therapy in those cases in which all disease has been removed and there is no histological evidence to suggest spread beyond the ovary.

TABLE 1.—*Classification of Ovarian Carcinoma.*[10]

Anatomic	*Histologic*
1. Tumor limited to ovary grossly, completely removed surgically, no evidence of microinvasion.	A. Well differentiated cystadenocarcinoma serous and/or mucinous.†
2. Tumor showing break through capsule, excrescences, infiltrated adhesions, grossly removed surgically, evidence of microinvasion of capsule, lymphatics, and blood vessels.	B. Poorly differentiated cystadenocarcinoma, serous and/or mucinous.
2S. Ruptured capsule or cyst with spillage of fluid.	C. Solid adenocarcinoma.
3. Tumor infiltrates other pelvic viscera as fallopian tubes, uterus, other ovary, bladder, rectum, sigmoid, pelvic peritoneum, grossly limited to pelvis, surgically not completely removed.	D. Endometrial type of adenocarcinoma.
4. Tumor has metastasized beyond pelvis.	E. Special tumors: Granulosa cell carcinoma, dysgerminoma, arrhenoblastoma, etc.

†Includes borderline carcinomas.

Stage 2. The 30 to 50 per cent incidence of local pelvic recurrence, makes postoperative irradiation advisable.[11] A midplane tumor dose of 5,000-5,500 rads,* delivered in five to six weeks at approximately 200 rads per day, is given through equally weighted anterior and posterior fields reaching from the pelvic floor to the pelvic brim and from sidewall to sidewall (Figure 1).

*All doses mentioned are tumor doses.

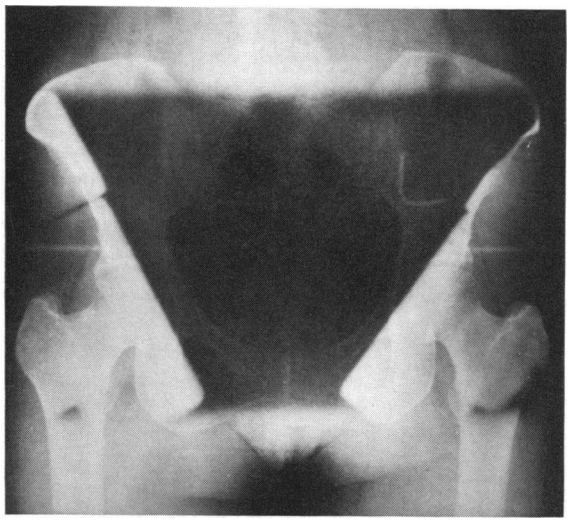
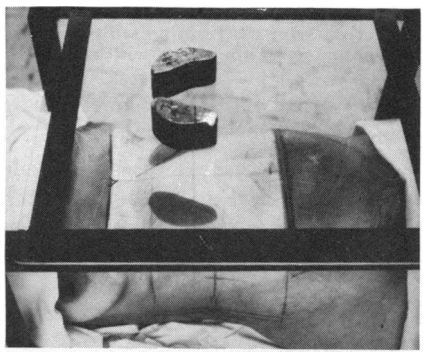


Figure 1.—Verification film of pelvis.



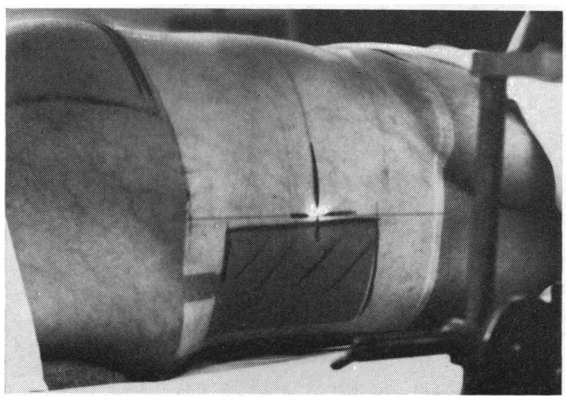


Figure 2.—Upper abdominal fields with kidney blocks in place. *Right,* anterior; *below,* left lateral.

Stage 2S. We have employed radioactive gold, radioactive chromic phosphate and several chemotherapeutic agents administered intraperitoneally at various times. There has been no detectable advantage in the use of the radioisotopes. Accordingly, we have advised installation of approximately 50 mg of triethylenthiophosphoramide dissolved in 100 ml of saline solution at the time of laparotomy just before closure. We rely upon this agent to prevent the

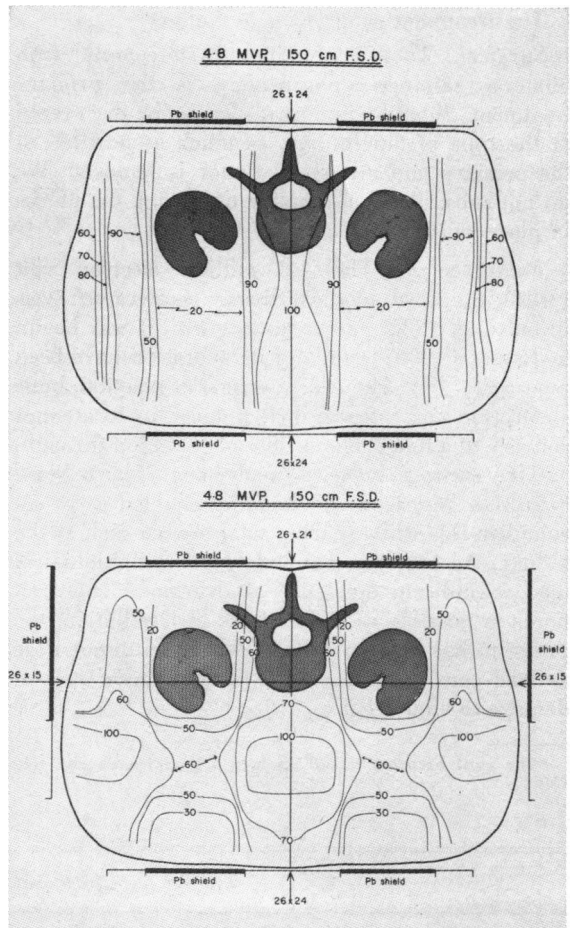


Figure 3. Isodose patterns for kidney shielding. The contour lines outline the distribution of the radiation in the patient with the two methods of kidney shielding; for example, if 4000 rads were delivered to the 100 per cent isodose contour, the 20 per cent contour would receive 800 rads.

Upper picture shows directly opposing anterior and posterior fields, 26 cm by 24 cm in size. Note the low dose volume anterior to the kidneys.

Lower picture: Four-field technique, 26 cm by 24 cm anterior and posterior fields and 26 cm by 15 cm opposing lateral fields. Note the improvement in dose distribution anterior to the kidneys.

MVP = Million volt peak. 4.8 MVP = Current operating energy of the Stanford medical linear accelerator. FSD = Focal-skin distance.

attachment and growth of cells floating free in the peritoneal cavity. These cells do not have a vascular supply and may be expected to be hypoxic and relatively radioresistant.[3] In a number of patients with this stage of disease local recurrence will develop within the pelvis and radiotherapy in this group of cases is given as outlined under Stage 2. An occasional patient has been treated with x-radiation to the entire peritoneal surface; but because of the complications to be mentioned later, we no longer advise this.

Stage 3. Postoperative radiotherapy improves the survival rate in the presence of residual disease in the pelvis.[1,4,7,9,11] Treatment is as outlined for Stage 2.

Stage 4. Treatment to the entire peritoneal cavity is required. The pelvis is treated first with fields similar to those described under Stage 2, but with a daily tumor dose of approximately 150 rads. If this daily dose is tolerated well, matching upper abdominal fields extending to the dome of the diaphragm are added after two weeks of pelvic treatment. The upper abdomen is treated through directly opposing equally weighted anterior and posterior fields to a midplane dose of 1,500-2,000 rads. The kidneys are then localized and protected by lead blocks 42 mm thick, and treatment is continued with an equally weighted four-field technique until a midplane dose of 3,500-4,500 rads has been delivered (Figure 2). This usually takes five to six weeks, making the overall treatment time approximately two months. As can be seen from Figure 3 the four-field technique minimizes the low dose volumes while providing adequate protection for the kidneys.

Palliation. Tumor doses of 2,000-3,000 rads are usually sufficient to control painful metastatic lesions

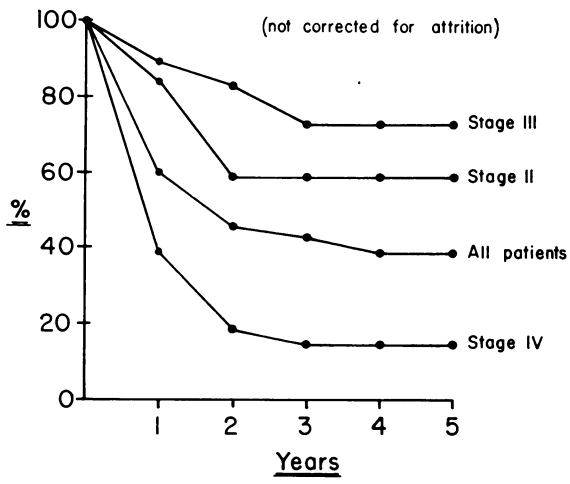


Chart 3.—Cumulative survival data, carcinoma of the ovary (Stanford University Medical Center, Division of Radiotherapy).

and bleeding, but have failed frequently to control ascites even when delivered to the whole abdomen.

Results

Survival data. Our results grouped by stages are shown in Chart 3. The projected four-year survival rate is 60 per cent in Stage 2, 73 per cent in Stage 3, and 15 per cent in Stage 4.

Hematologic effect. Pelvic irradiation was accompanied by a reduction in the white blood cell count below 3,000 cells per cu mm in only 18 per cent of the patients. The range of minimum counts was 2,000 to 5,800 cells per cu mm with a mean value of 3,900 cells per cu mm.

Irradiation of the entire abdomen resulted in a significant further reduction of the leukocyte count. Sixty per cent of the minimum values were below 3,000 cells per cu mm. The range of minimum counts was from 2,000 to 4,000 cells per cu mm with a mean of 2,800 cells. Depression in the leukocyte count was not associated with any early complication, and in no case was it necessary to interrupt treatment for more than a day or two.

Gastrointestinal effects. Although two-thirds of the patients were given medication for control of mild diarrhea and/or nausea, pelvic irradiation was tolerated well. Reduction of the daily dose because of gastrointestinal upset was rarely necessary.

Irradiation of the entire abdomen was not tolerated well. All patients required medication for control of diarrhea and/or nausea with vomiting. In two cases, late bowel complications developed, requiring surgical intervention in the absence of recurrent carcinoma.

Hepatic effects. Three patients died shortly after the conclusion of radiation therapy to the entire peritoneal cavity, with signs of hepatic failure, but no tumor could be demonstrated in the liver at postmortem examination. The histologic changes in the liver were unusual and will be reported in greater detail in a separate publication.

Renal effects. The dose received by the kidneys in the method described is of the order of 2,000 rads in three weeks. No case of clinical radiation nephritis has been apparent, and no significant changes have been seen on histologic examination of the kidneys of those patients who have been examined postmortem.

Discussion

The survival data presented are similar to those reported from other radiotherapy centers.* The results in Stages 2S and 3 confirm the advantages of

*References Nos. 1, 4, 7, 9, 10, 11.

postoperative radiation therapy and suggest that the combined surgical-radiation therapy approach offers the best chance for cure.

High dose irradiation, homogenously delivered to the entire peritoneal cavity, has not altered the outcome of Stage 4 poorly differentiated adenocarcinoma of the ovary. As has been reported by other investigators, patients with Stage 4 disease, the histologic features of which are well differentiated, may survive for long periods with minimal treatment, and we have not changed the outcome in this group.

In about 85 per cent of the patients with Stage 4 adenocarcinoma the disease was not controlled by our dose schedule. The mean survival following irradiation was six months. One must carefully consider the lack of palliation, the addition of radiation induced morbidity, the occurrence of late bowel complications, moderately severe leukopenia and the possibility of serious liver damage before advising intensive large field irradiation to Stage 4B ovarian cancer. It is our belief that in carefully selected patients with Stage 4 disease the lesion may be controlled and these are continuing in the program but the dose to the liver is limited to 3,000 rads.

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